

REMARKS

Applicants thank Examiner Le and SPE Campell for their helpful interview regarding the present application. The amendments herein and Applicants' responses to the outstanding rejections addresses the issues discussed during the interview.

Claim Amendments

Claims 1, 7-8 and 42 have been canceled herein. Claim 2 has been amended to remove aracytosine. No new matter has been added.

Claims 1-2, 7-8 and 42 are patentable over Schwartz.

Claims 1-2, 7-8 and 42 are rejected under 35 U.S.C. §103(a) as being unpatentable over Schwartz. Specifically, the Office Action states that Schwartz teaches modifying the dinucleotide CG with a modified C that can be cytosine arabinoside as evidenced by lines 5-15 of page 13 and Claim 4 of Schwartz.

Applicants respectfully disagree. Contrary to the position of the instant Office Action, Schwartz specifically defines a modified ISS on page 7, lines 12-15 as follows

We have discovered modified oligonucleotide sequences capable of modulating an immune response. Such oligonucleotide sequences comprise an immunostimulatory sequence (ISS) comprising a CG dinucleotide in which the C residue is modified by addition to C-5 and/or C-6 of an electron-withdrawing moiety ("modified ISS").

Schwartz goes on to describe that previous immunostimulatory sequences have comprised a hexamer sequence with a central CpG dinucleotide; however, the ISS of the present invention comprises any immunostimulatory sequence having the CG dinucleotide where the C5 and/or C6 positions of the C is modified with an electron-withdrawing group (see page 7, lines 22-25).

Schwartz then generically states that "a cytosine in the modified ISS can be substituted with a modified cytosine" including a laundry list of possible pyrimidine analogs (See page 13, lines 5-12). This paragraph includes pyrimidine analogs that do not have an electron withdrawing group at the C5 and/or C6 position (e.g. cytosine arabinoside). However, this is entirely inconsistent with the definition of the modified ISS of the invention and with the only

exemplified embodiment of the invention (Applicants note that the examples only use oligonucleotides wherein the C of the CG dinucleotide is 5-bromocytosine).

There are two possible ways to deal with this inconsistency. The first way is to conclude that the laundry list is governed by the specific definition and, thus, the analogs of the laundry list that are inconsistent with the specific definition should be excluded as neither supported nor enabled by the specification. Alternatively, the phrase "a cytosine in the modified ISS" could be interpreted to refer to a cytosine within the oligonucleotide but not in the CG dinucleotide. For example, using the sequence 5'-ACGTTCC-3' found on page 8 of Schwartz, the C at the 3rd position from the 5' end has an electron withdrawing group at the C5 and/or C6 position and the C at the 7th position from the 5' end could be cytosine arabinoside. Either way the laundry list of pyrimidines in Schwartz at best might be an invitation to experiment, without any reasonable expectation of success.

Regardless, the only fair reading of Schwartz limits the oligonucleotides solely to the modification of C of the CG dinucleotide at the C-5/6 positions with an electron withdrawing group. However, without conceding to the correctness of the Examiner's position but in order to expedite prosecution of the instant application, aracytosine has been removed from Claim 2. Applicants reserve the right to prosecute the deleted subject matter at a later date or in a timely filed continuation application.

Accordingly, the claimed subject matter is patentable over Schwartz. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1-2, 7-8 and 41-42 are patentable over Nguyen in view of Schwartz

Claims 1-2, 7-8 and 41-42 are rejected under 35 U.S.C. §103(a) as being unpatentable over Nguyen in view of Schwartz.

As stated above, Schwartz teaches a modified ISS comprising a CG dinucleotide in which the C residue is modified by addition to C-5 and/or C-6 of an electron withdrawing (hydrogen bond acceptor) group.

Nguyen teaches the incorporation of modified C bases into oligonucleotides to obtain DNA duplexes with a thermal stability independent of their base content. Nguyen goes on to state that these oligonucleotides have properties that make them useful in reverse hybridization approaches, using a large number of sequences immobilized as a two-dimensional matrix for

simple and fast analysis of nucleic acid sequences, or in biochemical techniques, such as random priming, for the preparation of DNA and labeling DNA fragments by an enzymatic method.

The mere fact that the references could be combined to arrive at the claimed invention is not sufficient. The prior art must suggest the desirability of the combination. Schwartz teaches a very specific modification of an oligonucleotide comprising a CG dinucleotide. Schwartz does not teach any other modification to the CG dinucleotide or that any other modification would still maintain the immunostimulatory activity of the CG dinucleotide.

Nguyen fails to teach what Schwartz lacks. Nguyen does not teach the immune stimulatory properties of the disclosed oligonucleotide or provide any suggestion or motivation to modify the oligonucleotides as taught by Schwartz. One skilled in the art would not have been motivated, with a reasonable expectation of success, to combine the teachings of Schwartz with Nguyen to arrive at the instantly claimed invention. In fact, that motivation is provided only through hindsight in view of the present specification, which of course is not permitted.

Since there is no mention in either Schwartz or Nguyen of the desirability of combining their teachings, Claims 1-2, 7-8 and 41-42 are patentable over Nguyen in view of Schwartz. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1-2 and 40 are patentable over Tardy-Planechaud in view of Schwartz

Claims 1-2 and 42 are rejected under 35 U.S.C. §103(a) as being unpatentable over Tardy-Planechaud in view of Schwartz.

As stated above, Schwartz teaches a modified ISS comprising a CG dinucleotide in which the C residue is modified by addition to C-5 and/or C-6 of an electron withdrawing (hydrogen bond acceptor) group, regardless of the nature of the sugar to which it is attached.

Tardy-Planechaud teaches the influence of specific 5-(hydroxymethyl)cytosine (^{hm}C) residues, which result from the oxidation of the 5-methyl group of 5-methylcytosine, on enzymatic cleavage of oligodeoxynucleotides by the methylation-sensitive restriction endonucleases *MspI* and *HpaII*.

The mere fact that the references could be combined to arrive at the claimed invention is not sufficient. The prior art must suggest the desirability of the combination. Schwartz teaches a very specific modification of an oligonucleotide comprising a CG dinucleotide. Schwartz does

not teach any other modification to the CG dinucleotide or that any other modification would still maintain the immunostimulatory activity of the CG dinucleotide.

Tardy-Planchaud fails to teach what Schwartz lacks. Tardy-Planechaud doesn't teach the immune stimulatory properties of the disclosed oligonucleotide or provide any suggestion or motivation to modify the oligonucleotides of Schwartz. In fact, the initial cytosine residue disclosed in Tardy-Planechaud is 5-methylcytosine which is not immunostimulatory. One skilled in the art would not have been motivated, with a reasonable expectation of success, to combine the teachings of Schwartz with Tardy-Planechaud to arrive at the instantly claimed invention. In fact, that motivation is provided only through hindsight in view of the present specification, which of course is not permitted.

Since there is no mention in either Schwartz or Tardy-Planechaud of the desirability of combining their teachings, Claims 1-2 and 40 are patentable over Tardy-Planechaud in view of Schwartz. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1-2 and 39 are patentable over Kreutzer et al. in view of Schwartz

Claims 1-2 and 39 are rejected under 35 U.S.C. §103(a) as being unpatentable over Kreutzer et al. in view of Schwartz.

As stated above, Schwartz teaches a modified ISS comprising a CG dinucleotide in which the C residue is modified by addition to C-5 and/or C-6 of an electron withdrawing (hydrogen bond acceptor) group, regardless of the nature of the sugar to which it is attached. The 5'-hydroxycytosine of Kreutzer has an added electron donating group (hydrogen bond donor).

The mere fact that the references could be combined to arrive at the claimed invention is not sufficient. The prior art must suggest the desirability of the combination. Schwartz teaches a very specific modification of an oligonucleotide comprising a CG dinucleotide. Schwartz does not teach any other modification to the CG dinucleotide or that any other modification would still maintain the immunostimulatory activity of the CG dinucleotide.

Kreutzer fails to teach what Schwartz lacks. Kreutzer describes the most common base substitutions arising from oxidative damage of DNA. Kreutzer does not teach the immune stimulatory properties of the disclosed oligonucleotide or provide any suggestion or motivation to modify the oligonucleotides of Schwartz. One skilled in the art would not have been motivated, with a reasonable expectation of success, to combine the teachings of Schwartz with

Kreutzer to arrive at the instantly claimed invention. In fact, that motivation is provided only through hindsight in view of the present specification, which of course is not permitted.

Since there is no mention in either Schwartz or Kreutzer of the desirability of combining their teachings, Claims 1-2 and 39 are patentable over Kreutzer in view of Schwartz. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 2 and 43 are patentable over Merigan, Jr. in view of Schwartz

Claims 2 and 43 are rejected under 35 U.S.C. §103(a) as being unpatentable over Merigan, Jr. in view of Schwartz.

As stated above, Schwartz teaches a modified ISS comprising a CG dinucleotide in which the C residue is modified by addition to C-5 and/or C-6 of an electron withdrawing (hydrogen bond acceptor) group, regardless of the nature of the sugar to which it is attached.

Merigan, Jr. teaches the incorporation of modified C bases into oligonucleotides to obtain DNA duplexes with a thermal stability independent of their base content. Merigan, Jr. goes on to state that these oligonucleotides have properties that make them useful in reverse hybridization approaches, using a large number of sequences immobilized as a two-dimensional matrix for simple and fast analysis of nucleic acid sequences, or in biochemical techniques, such as random priming, for the preparation of DNA and labeling DNA fragments by an enzymatic method.

The mere fact that the references could be combined to arrive at the claimed invention is not sufficient. The prior art must suggest the desirability of the combination. Contrary to the assertion within the Office Action, Schwartz does not suggest the substitution of cytosine for any modified pyrimidine or pyrimidine analog. Schwartz teaches a very specific modification of an oligonucleotide comprising a CG dinucleotide. Schwartz does not teach any other modification to the CG dinucleotide or that any other modification would still maintain the immunostimulatory activity of the CG dinucleotide.

Merigan, Jr. fails to teach what Schwartz lacks. Merigan, Jr. doesn't teach the immune stimulatory properties of the disclosed oligonucleotide or provide any suggestion or motivation to modify the oligonucleotides of Schwartz. In fact, Merigan, Jr. does not disclose an oligonucleotide having a CG dinucleotide. Rather, Merigan Jr. merely teaches the preparation of polynucleotides having phosphorothioate linkages, and provides no teaching that 4-thiouracil could be substituted for the C of the CG dinucleotide and still have immune stimulation

properties. One skilled in the art would not have been motivated, with a reasonable expectation of success, to combine the teachings of Schwartz with Merigan, Jr. to arrive at the instantly claimed invention. In fact, that motivation is provided only through hindsight in view of the present specification, which of course is not permitted.

Since there is no mention in either Schwartz or Merigan, Jr. of the desirability of combining their teachings, Claims 1-2, 7-8 and 41-42 are patentable over Merigan, Jr. in view of Schwartz. Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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